EXHIBIT O

MFIA MEDIA FREEDOM & INFORMATION ACCESS CLINIC

ABRAMS INSTITUTE FOR FREEDOM OF EXPRESSION

Yale Law School

FREEDOM OF INFORMATION ACT APPEAL

April 29, 2021

Director, Office of the Executive Secretariat
U.S. Food & Drug Administration
5630 Fishers Lane
Room 1050
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

Re: Appeal of FOIA Request Nos. 2019-4472, 2019-4465, 2019-4457, 2019-4455, and 2019-4428

Dear FOIA Appeals Officer,

We, the Yale Law School Media Freedom & Information Access Clinic, represent Dr. G. Caleb Alexander in connection with the above-captioned requests under the Freedom of Information Act ("FOIA"), 5 U.S.C. 552 *et seq*. This letter constitutes an administrative appeal of the U.S. Food and Drug Administration ("FDA")'s constructive denial of Dr. Alexander's requests.

I. Factual and Procedural History

On May 21, 2019, Dr. Alexander submitted six FOIA requests to the FDA. True and correct copies of these requests are attached as Exhibits A-F.

These requests sought records relating to the FDA's decision to impose, modify, retain, or terminate Risk Evaluation and Mitigation Strategy (REMS) requirements for six drugs: zolpidem, varenicline, prasugrel, mifepristone, clopidogrel, and salmeterol-fluticasone. These requests identified specific time periods for responsive records.

On May 22, 2019, Dr. Alexander received an email from FDA_FOI@fda.gov acknowledging receipt of his salmeterol-fluticasone request. On May 23, 2019, Dr. Alexander received emails from FDA_FOI@fda.gov acknowledging receipt of his mifepristone, clopidogrel, prasugrel, zolpidem, and varenicline requests. True and correct copies of these emails are attached as Exhibits G-L. These emails assigned Dr. Alexander's requests the following reference numbers:

- Zolpidem: 2019-4472
- Prasugrel: 2019-4465
- Mifepristone: 2019-4457
- Clopidogrel: 2019-4455
- Salmeterol-Fluticasone: 2019-4428
- Varenicline: 2019-4458

These emails specified that the FDA "will respond as soon as possible" to Dr. Alexander's requests and provided no indication that the FDA could not respond to them within the statutory deadline.

The FDA failed to respond to Dr. Alexander's requests within the statutory deadline. So in August 2019, Dr. Alexander contacted the Center for Drug Evaluation and Research ("CDER") FOIA Office via telephone regarding the FDA's delay. The CDER FOIA Office told Dr. Alexander that his mifepristone request was in the fourth or fifth position in the complex queue and that a response might be expected within a matter of weeks or months.

On August 17, 2020, the FDA responded to Dr. Alexander's varenicline request. The FDA's cover letter to its August 17, 2020 response did not state that the FDA had withheld any documents in their entirety. Most of the documents it provided were publicly available. The FDA also did not provide several documents Dr. Alexander specifically requested. Missing from the production were, among other documents:

- "FDA's initial evaluation assessing whether a REMS is needed for varenicline";
- "the May 2008 FDA letter to Pfizer requiring a REMS and issuing a post marketing requirement for a clinical trial";
- "[t]he 18-month [REMS Assessment] Report submitted [by Pfizer] in or around April 2011";
- "the 3-year [REMS Assessment] Report submitted [by Pfizer] in or around October 2012";
- "the 7-year [REMS Assessment] Report submitted [by Pfizer] in or around October 2016";
- "Pfizer's proposed modifications, including elimination, to the approved REMS plan . . . including those submitted on November 8, 2013 and September 3, 2014"; and
- "FDA's review of Pfizer's 18 Month Report, 3 Year Report, and 7 Year Report."

On November 17, 2020, Dr. Alexander administratively appealed the FDA's response to his varenicline request.

On November 18, 2020, the FDA acknowledged receipt of Dr. Alexander's administrative appeal to the FDA's determination on his varenicline request and assigned it appeal file number 21-0006AA. The FDA specified that "[p]ursuant to 5 U.S.C. § 552(a)(6)(B)(i) and 5 U.S.C. § 552(a)(6)(B)(iii) of the FOIA and 45 C.F.R. 5.24(f) of the HHS FOIA regulations, [Dr. Alexander's] appeal falls under the 'unusual circumstances' in that our office will need to consult

with another office that has substantial interest in the determination of the appeal. The actual processing time will depend on the complexity of the issues presented in the appeal."

On November 20, 2020, the FDA emailed Dr. Alexander, indicating that "CDER is going to reopen [Dr. Alexander's] request for processing" and asking whether Dr. Alexander "[w]ould like to withdraw the appeal until CDER sends another response with new appeal rights or keep it open." On November 22, 2020, Dr. Alexander responded to this email and indicated that he "would like to continue to keep the appeal that [he] ha[d] filed open."

By February 2021, the FDA had not responded to Dr. Alexander's zolpidem, prasugrel, mifepristone, clopidogrel, and salmeterol-fluticasone requests, and had neither provided additional documents for Dr. Alexander's varenicline request nor responded to his appeal. Thus, on February 26, 2021, we contacted Sudarshini Satchi, CDER Freedom of Information Branch Chief, to again bring the delay in the FDA's response to the agency's attention and prompt the FDA to produce responsive documents. On March 3, 2021, Guruprasad Udapi, a Supervisory Government Information Specialist at CDER, responded to our email, noting that CDER responds to requests in "date order priority" and that there were approximately 200 FOIA requests with priority over Dr. Alexander's requests. Mr. Udapi estimated that it would take 24 months to process complex requests like those of Dr. Alexander. A true and correct copy of this email exchange is attached as Exhibit M.

On March 11, 2021, we responded to Mr. Udapi requesting a call to discuss how to resolve the delay in processing Dr. Alexander's requests. The FDA did not respond to this email. A true and correct copy of this email is attached as Exhibit N.

On March 22, 2021, we sent a second email to Mr. Udapi requesting a call to discuss how to resolve the delay in processing Dr. Alexander's requests, particularly in light of the FDA's shifting and inconsistent positions on how long it would take to respond to them. The FDA did not respond to this email. A true and correct copy of this email is attached as Exhibit O.

The FDA still has not responded to Dr. Alexander's zolpidem, prasugrel, mifepristone, clopidogrel, and salmeterol-fluticasone requests submitted in May 2019, and has neither provided additional documents for Dr. Alexander's varenicline request nor responded to his November 2020 administrative appeal.

II. Argument

FOIA requires agencies to "make a determination" on any request within twenty business days of its receipt. 5 U.S.C. § 552(a)(6)(A)(i). This determination "must be more than just an initial statement that the agency will generally comply with a FOIA request and will produce non-exempt documents and claim exemptions in the future." *Citizens for Resp. & Ethics in Wash. v. Fed. Election Comm'n*, 711 F.3d 180, 188 (D.C. Cir. 2013). The agency "must at least (i) gather and review the documents; (ii) determine and communicate the scope of the documents it intends to produce and withhold, and the reasons for withholding any documents; and (iii) inform the requester that it can appeal whatever portion of the 'determination' is adverse." *Id.*

In this case, the FDA failed to make a "determination" concerning Dr. Alexander's zolpidem, prasugrel, mifepristone, clopidogrel, and salmeterol-fluticasone requests. The FDA acknowledged receipt of Dr. Alexander's salmeterol-fluticasone request on May 22, 2019 and his zolpidem, prasugrel, mifepristone, and clopidogrel requests on May 23, 2019. Dr. Alexander still has not received responses to these requests, more than 700 days later. The FDA is in violation of its statutory duties under FOIA. *See* 5 U.S.C. § 552(a)(6)(A)(i), (B)(i).

III. Conclusion

By failing to provide a determination with respect to Dr. Alexander's zolpidem, prasugrel, mifepristone, clopidogrel, and salmeterol-fluticasone requests within the statutory deadline, the FDA is in violation of its obligations under FOIA. Dr. Alexander respectfully requests that you direct the agency to make a determination with respect to Dr. Alexander's zolpidem, prasugrel, mifepristone, clopidogrel, and salmeterol-fluticasone requests as soon as possible, but in any case no more than twenty business days from the date this administrative appeal is received. 5 U.S.C. § 552(a)(6)(A)(ii).

If you have any questions regarding these appeals, please do not hesitate to call me at (520) 488-0486 or email me at stephen.stich@ylsclinics.org. I look forward to your response.

Sincerely,

Stephen Stich
Media Freedom and Information Access Clinic
Yale Law School
P.O. Box 208215
New Haven, CT 06520-8215
(520) 488-0486
stephen.stich@ylsclinics.org

EXHIBIT A

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Drug Safety and Effectiveness

May 21, 2019

Food and Drug Administration
Division of Freedom of Information
Office of Shared Services
Office of Public Information and Library Services
12420 Parklawn Drive
ELEM-1029
Rockville, MD 20857

Re: FREEDOM OF INFORMATION ACT REQUEST

To Whom It May Concern:

My name is Caleb Alexander. I am a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health. This letter constitutes a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552, for records related to the FDA REMS program related to zolpidem.

Background

Risk Evaluation and Mitigation Strategies (REMS) of the Food and Drug Administration (FDA) represent an important regulatory tool that the FDA uses to optimize the safe use of approved therapeutics. As with any risk evaluation and mitigation program, the success of the REMS depends critically upon the quality and comprehensiveness of data that is used to guide regulatory decision-making. While the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversight of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

This request concerns the REMS for a particular drug, zolpidem, marketed under the brand name Zolpimist by Aytu BioScience ("Aytu") and under the brand name Edluar by Meda Pharmaceuticals ("Meda"). Zolpimist (Oral Spray) and Edluar (sublingual tablets) were subject to a product-specific REMS from 2008 to 2011 that required a medication guide. The REMS was instituted because of the complex sleep-related behaviors and severe anaphylactic reactions associated with using these zolpidem products. I am interested in the Zolpidem REMS documents to study the rationale that led to the FDA's decision to release zolpidem from its REMS and to

better understand why Zolpimist and Edluar were subject to a REMS while other products in its class (e.g. Ambien) were not.

Requested Records

I seek release of the following:

Any records relating to the REMS for zolpidem(Zolpimist/Edluar) from 2007 through 2013 including:

1. All correspondence between the FDA and Aytu, Meda or any NDA for zolpidem (Zolpimist, Eluar) and any other manufacturers of this product including:
    a. FDA's initial evaluation assessing whether a REMS is needed for zolpidem
    b. FDA's written correspondence explaining that a REMS is necessary
    c. Aytu's, Meda's and any other manufactuer of this product's proposed REMS plans, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. Aytu's, Meda's and any other manufactuer of this product's REMS supporting documents, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the proposed REMS plan
    f. FDA's evaluation of the proposed supporting document
    g. Aytu's, Meda's and any other manufactuer of this product's proposed modifications, including elimination, to the approved REMS plan
    h. FDA's correspondence to Aytu and/or Meda and/or and any other manufactuer of this product approving or denying the modifications, including elimination, to the approved REMS plan
    i. Any explanations by the FDA regarding their final decision about the REMS plan
2. All REMS Assessment Reports submitted by Aytu, Meda and any other manufactuer of this product to the FDA, including:
    a. The first Assessment Report submitted due on September 13, 2010
    b. The Interim Assessment with Patient KAB due on June 11, 2011,
    c. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to Aytu, Meda and any other manufactuer of this produc between December 2008 and September 2011.
4. Any FDA REMS Modification Review reports sent to Aytu, Meda and any other manufactuer of this product between December 2008 and September 2011 including the October 2010 review
5. The FDA's evaluation assessing whether a REMS is needed for zolpidem, including any FDA memoranda, and the written information used by FDA in the assessment, including any data.

6. Any subsequent communication between the FDA and Aytu and/or Meda and/or and any other manufactuer of this product relating to all of the above

I request that all of these documents be produced in their native electronic formats with any attached metadata included, so long as such electronic files can be opened using standard commercially available software. If the files cannot be produced in this manner, I request that records be produced in an alternative electronic format that is text-searchable. With respect to databases, spreadsheets or similar organized sets of data, I request that the records be produced in .xls or .csv format. *See* 5 U.S.C. § 552(a)(3)(B).

Application for Expedited Processing

I request expedited processing for this request pursuant to 5 U.S.C. § 552(a)(6)(E) and 21 C.F.R. § 20.44(a)(2).

Expedited processing is appropriate here because a compelling need exists for the disclosure of the requested information. Shedding light on FDA's internal processes for instituting (and releasing) REMS is likely to have significant public health benefits, thereby reducing threats to the life or physical safety of all individuals using FDA-approved drugs. The public interest is heightened because REMS are implemented for unusually dangerous drugs where there is a concern "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1. Clinicians, researchers, and the public at large will benefit from prompt access to the requested information, to ensure that the zolpidem REMS and other REMS function well and that patients are not being harmed by REMS that are over- or underprotective.

Pursuant to 5 U.S.C. § 552(a)(6)(E)(vi) and 21 C.F.R. § 20.44(a)(2), I certify that the information in this request concerning the reasons for expedited processing is true and correct to the best of my knowledge and belief.

Application for Waiver of Fees

Pursuant to 5 U.S.C. § 552(a)(4)(A)(iii) and 21 C.F.R. § 20.46, I request waiver of fees incurred in connection with searching and copying in responding this request. I am requesting the waiver on the grounds that disclosure of the requested information is in the public interest because it is likely to contribute significantly to public understanding of the operations and activities of the government and is not primarily in the commercial interest of the requester.

Disclosure is in the public interest:

Disclosure is in the public interest pursuant to 21 CFR § 20.46(b)(1) and (2) because this request will shed light into operations or activities of the FDA that are not already public knowledge. As noted above in the Background section, while the FDA has taken important steps during the past

decade to increase transparency regarding some elements of REMS programs, remarkably little is known about how REMS programs are developed, implemented, and monitored, including regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversite of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

The circumstances surrounding the FDA's decision to create a REMS for zolpidem are not public knowledge. As noted above in the Background section, I am interested in the Zolpidem REMS documents to study the rationale that led to the FDA's decision to release zolpidem from its REMS and to better understand why Zolpimist and Edluar were subject to a REMS while other products in its class (e.g. Ambien) were not.

Disclosure is also in the public interest pursuant to 21 CFR § 20.46(b)(3) and (4) because I plan to disseminate the information I obtain from this request to the public through publication in widely distributed, high-impact, peer-reviewed medical and public health journals, as well as other media. I have an established track record of such publications, including publications based on FOIA requests to FDA. Exemplary high-impact publications based on my investigations include

- Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products. *JAMA.* 2019;321(7):676–685. doi:10.1001/jama.2019.0235
- Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med.* 2018;178(11):1451–1457. doi:10.1001/jamainternmed.2018.3931
- Qato DM, Alexander GC. Post-Marketing Drug Safety and the Food and Drug Administration's Risk Evaluation and Mitigation Strategies. *JAMA*. 2011;306:1595-1596.

The requester has no commercial interest in the information sought:

I have no commercial interest in the information sought. 45 C.F.R. § 5.54(b)(3). I am not in the business of developing or selling new drugs or biologics, and I do not stand to make a profit from the disclosure of the requested information. I have no commercial interest in these records, but rather I aim to facilitate and conduct rigorous, objective, and fair evaluation of the information sought in furtherance of public knowledge and public health.

For these reasons, a public interest waiver of fees is appropriate here. I therefore respectfully request that all fees related to the search, review, and duplication of the requested records be waived. If the search and review fees will not be waived, I ask that you contact me at the email address listed below should the estimated fees resulting from this request exceed $100.

Conclusion

Pursuant to applicable statutes and regulations, I anticipate a determination regarding expedited processing within 10 days. *See* 5 U.S.C. § 552(a)(6)(E)(ii); 21 C.F.R. § 20.44(a)(2).

If my request is denied in whole or in part, please justify all withholdings and redactions by reference to specific FOIA exemptions. I expect the release of all segregable portions of otherwise exempt material, see 5 U.S.C. § 552(b), and reserve the right to appeal a decision to withhold any information or deny a waiver of fees.

Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street W6035
Baltimore, MD 21205
Phone: 410 955 8168
Fax: 410 955 0863
Email: galexan9@jhmi.edu

Please communicate any questions you may have by phone or email, rather than regular mail. Also, if the requested records cannot be provided by email, please notify me as soon as they are available and I will consider arranging to collect them by courier to avoid additional delay.

Your prompt attention to this request is greatly appreciated.

Respectfully,

G Caleb Alexander

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine

EXHIBIT B

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Drug Safety and Effectiveness

May 21, 2019

Food and Drug Administration
Division of Freedom of Information
Office of Shared Services
Office of Public Information and Library Services
12420 Parklawn Drive
ELEM-1029
Rockville, MD 20857

Re: FREEDOM OF INFORMATION ACT REQUEST

To Whom It May Concern:

My name is Caleb Alexander. I am a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health. This letter constitutes a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552, for records related to the FDA REMS program related to prasugrel.

Background

Risk Evaluation and Mitigation Strategies (REMS) of the Food and Drug Administration (FDA) represent an important regulatory tool that the FDA uses to optimize the safe use of approved therapeutics. As with any risk evaluation and mitigation program, the success of the REMS depends critically upon the quality and comprehensiveness of data that is used to guide regulatory decision-making. While the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversight of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

This request concerns the REMS for a particular drug, prasugrel, marketed under the brand name Effient by Eli Lilly ("Lilly"). Effient (Prasugrel) was subject to a REMS from 2009 to 2012 that included a medication guide and a communication plan. The basis for this product-specific REMS was to mitigate the risk of major bleeding associated with Effient. After the REMS was discontinued, the FDA maintained the requirement for a medication guide. We are interested in the Prasugrel REMS documents to study the rationale that led to the FDA's decision to release Prasugrel from its REMS and to evaluate how effective the medication guide is, and the communication plan was, at mitigating risks associated with Effient.

Requested Records

I seek release of the following:

Any records relating to the REMS for prasugrel (Effient) from 2008 to 2014 including:

1. All correspondence between the FDA and Lilly and any other manufacturer of this product including:
    a. FDA's initial evaluation assessing whether a REMS is needed for prasugrel
    b. FDA's written correspondence explaining that a REMS is necessary
    c. Lilly's and any other manufacturer of this product's proposed REMS plan, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. Lilly's and any other manufacturer of this product's REMS supporting document, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the proposed REMS plan
    f. FDA's evaluation of the proposed supporting document
    g. Lilly's and any other manufacturer of this product's proposed modifications, including elimination, to the approved REMS plan
        i. including the proposed modified REMS submitted on June 15, 2011
    h. FDA's correspondence to Lilly and any other manufacturer of this product approving or denying the modifications, including elimination, to the approved REMS plan
    i. Any explanations by the FDA regarding their final decision about the REMS plan
2. All REMS Assessment Reports submitted by Lilly and any other manufacturer of this product to the FDA, including:
    a. The REMS Assessment Report due January 31, 2011
    b. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to Lilly and any other manufacturer of this product, including an review of the report due January 31, 2011
4. Any FDA REMS Modification Review reports sent to Lilly and any other manufacturer of this product between July 2009 and March 2012, including those approved on April 16, 2010 and December 6, 2010
5. The FDA's evaluation assessing whether a REMS is needed for prasugrel, including any FDA memoranda, and the written information used by FDA in the assessment, including any data.
6. Any subsequent communication between the FDA and Lilly and any other manufacturer of this product relating to all of the above

I request that all of these documents be produced in their native electronic formats with any attached metadata included, so long as such electronic files can be opened using standard

commercially available software. If the files cannot be produced in this manner, I request that records be produced in an alternative electronic format that is text-searchable. With respect to databases, spreadsheets or similar organized sets of data, I request that the records be produced in .xls or .csv format. *See* 5 U.S.C. § 552(a)(3)(B).

Application for Expedited Processing

I request expedited processing for this request pursuant to 5 U.S.C. § 552(a)(6)(E) and 21 C.F.R. § 20.44(a)(2).

Expedited processing is appropriate here because a compelling need exists for the disclosure of the requested information. Shedding light on FDA's internal processes for instituting (and releasing) REMS is likely to have significant public health benefits, thereby reducing threats to the life or physical safety of all individuals using FDA-approved drugs. The public interest is heightened because REMS are implemented for unusually dangerous drugs where there is a concern "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1. Clinicians, researchers, and the public at large will benefit from prompt access to the requested information, to ensure that the prasugrel REMS and other REMS function well and that patients are not being harmed by REMS that are over- or underprotective.

Pursuant to 5 U.S.C. § 552(a)(6)(E)(vi) and 21 C.F.R. § 20.44(a)(2), I certify that the information in this request concerning the reasons for expedited processing is true and correct to the best of my knowledge and belief.

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Disclosure is in the public interest:

Disclosure is in the public interest pursuant to 21 CFR § 20.46(b)(1) and (2) because this request will shed light into operations or activities of the FDA that are not already public knowledge. As noted above in the Background section, while the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known about how REMS programs are developed, implemented, and monitored, including regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversite of prescription

drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

The circumstances surrounding the FDA's decision to create a REMS for prasugrel are not public knowledge. As noted above in the Background section, I am interested in the Prasugrel REMS documents to study the rationale that led to the FDA's decision to release Prasugrel from its REMS and to evaluate how effective the medication guide is, and the communication plan was, at mitigating risks associated with Effient.

Disclosure is also in the public interest pursuant to 21 CFR § 20.46(b)(3) and (4) because I plan to disseminate the information I obtain from this request to the public through publication in widely distributed, high-impact, peer-reviewed medical and public health journals, as well as other media. I have an established track record of such publications, including publications based on FOIA requests to FDA. Exemplary high-impact publications based on my investigations include

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The requester has no commercial interest in the information sought:

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Conclusion

Pursuant to applicable statutes and regulations, I anticipate a determination regarding expedited processing within 10 days. *See* 5 U.S.C. § 552(a)(6)(E)(ii); 21 C.F.R. § 20.44(a)(2).

If my request is denied in whole or in part, please justify all withholdings and redactions by reference to specific FOIA exemptions. I expect the release of all segregable portions of otherwise exempt material, see 5 U.S.C. § 552(b), and reserve the right to appeal a decision to withhold any information or deny a waiver of fees.

Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

G. Caleb Alexander, MD, MS
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Department of Epidemiology
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Baltimore, MD 21205
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Email: galexan9@jhmi.edu

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Your prompt attention to this request is greatly appreciated.

Respectfully,

G Caleb Alexander

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine

EXHIBIT C

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Drug Safety and Effectiveness

May 21, 2019

Food and Drug Administration
Division of Freedom of Information
Office of Shared Services
Office of Public Information and Library Services
12420 Parklawn Drive
ELEM-1029
Rockville, MD 20857

Re: FREEDOM OF INFORMATION ACT REQUEST

To Whom It May Concern:

My name is Caleb Alexander. I am a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health. This letter constitutes a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552, for records related to the FDA REMS program related to Mifepristone.

Background

Risk Evaluation and Mitigation Strategies (REMS) of the Food and Drug Administration (FDA) represent an important regulatory tool that the FDA uses to optimize the safe use of approved therapeutics. As with any risk evaluation and mitigation program, the success of the REMS depends critically upon the quality and comprehensiveness of data that is used to guide regulatory decision-making. While the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversight of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

This request concerns the REMS for a particular drug, mifepristone, marketed under the brand name Mifeprex by Danco Laboratories. Mifeprex (Mifepristone) has been subject to one of the most restrictive REMS since 2011; the REMS has included Elements to Assure Safe Use (ETASU). The basis for this REMS is to ensure that Mifeprex is only prescribed by REMS-certified prescribers, that it is only dispensed in approved settings and that patients are informed of the risks, including bleeding, infection, and ectopic pregnancy, associated with taking Mifeprex. I am interested in: (1) the rationale for mandating the REMS, specifically as an ETASU; (2) how safety of Mifeprex (Mifepristone) has been monitored since the REMS was implemented; and (3)

what safety concerns, if any, have been discovered that support the continuation of this restrictive REMS. Mifepristone is of significant public health importance given its FDA-approved indication for use, in combination with misoprostol, to safely terminate early pregnancies.

Requested Records

I seek release of the following:

Any records relating to the REMS for Mifepristone/Mifeprex/RU-486 from 2010 to present including:

1. All correspondence between the FDA and Danco Laboratories and any other manufacturers of this product including:
    a. FDA's initial evaluation assessing whether a REMS is needed for Mifepristone
    b. FDA's written correspondence explaining that a REMS is necessary
    c. Danco Laboratories' and any other manufacturers of this product's proposed REMS plan, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. Danco Laboratories' and any other manufacturers of this product's REMS supporting document, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the proposed REMS plan
    f. FDA's evaluation of the proposed supporting document
    g. Danco Laboratories' and any other manufacturers of this product's proposed modifications, including elimination, to the approved REMS plan
    h. FDA's correspondence to Danco Laboratories and any other manufacturers of this product approving or denying the modifications, including elimination, to the approved REMS plan
    i. Any explanations by the FDA regarding their final decision about the REMS plan
2. All REMS Assessment Reports submitted by Danco Laboratories and any other manufacturers of this product to the FDA, including:
    a. The 1-year Report submitted in 2012, the 4-year Report submitted in 2015, and the 7-year Report submitted in 2018.
    b. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to Danco Laboratories and any other manufacturers of this product
4. Any FDA REMS Modification Review reports sent to Danco Laboratories and any other manufacturers of this product since June 2011
5. The FDA's evaluation assessing whether a REMS is needed for mifepristone, including any FDA memoranda, and the written information used by FDA in the assessment, including any data.

6. Any subsequent communication between the FDA and Danco Laboratories and any other manufacturers of this product relating to all of the above

I request that all of these documents be produced in their native electronic formats with any attached metadata included, so long as such electronic files can be opened using standard commercially available software. If the files cannot be produced in this manner, I request that records be produced in an alternative electronic format that is text-searchable. With respect to databases, spreadsheets or similar organized sets of data, I request that the records be produced in .xls or .csv format. *See* 5 U.S.C. § 552(a)(3)(B).

Application for Expedited Processing

I request expedited processing for this request pursuant to 5 U.S.C. § 552(a)(6)(E) and 21 C.F.R. § 20.44(a)(2).

Expedited processing is appropriate here because a compelling need exists for the disclosure of the requested information. Shedding light on FDA's internal processes for instituting (and releasing) REMS is likely to have significant public health benefits, thereby reducing threats to the life or physical safety of all individuals using FDA-approved drugs. The public interest is heightened because REMS are implemented for unusually dangerous drugs where there is a concern "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1. Clinicians, researchers, and the public at large will benefit from prompt access to the requested information, to ensure that the Mifepristone REMS and other REMS function well and that patients are not being harmed by REMS that are over- or underprotective.

Pursuant to 5 U.S.C. § 552(a)(6)(E)(vi) and 21 C.F.R. § 20.44(a)(2), I certify that the information in this request concerning the reasons for expedited processing is true and correct to the best of my knowledge and belief.

Application for Waiver of Fees

Pursuant to 5 U.S.C. § 552(a)(4)(A)(iii) and 21 C.F.R. § 20.46, I request waiver of fees incurred in connection with searching and copying in responding this request. I am requesting the waiver on the grounds that disclosure of the requested information is in the public interest because it is likely to contribute significantly to public understanding of the operations and activities of the government and is not primarily in the commercial interest of the requester.

Disclosure is in the public interest:

Disclosure is in the public interest pursuant to 21 CFR § 20.46(b)(1) and (2) because this request will shed light into operations or activities of the FDA that are not already public knowledge. As noted above in the Background section, while the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known about how REMS programs are developed, implemented, and monitored, including regarding the assessments that manufacturers of specific therapeutics have performed, or how

these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversite of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

The circumstances surrounding the FDA's decision to create a REMS for mifepristone are not public knowledge. As noted above in the Background section, I and the public at large are interested in: (1) the rationale for mandating the REMS, specifically as an ETASU; (2) how safety of Mifeprex (Mifepristone) has been monitored since the REMS was implemented; and (3) what safety concerns, if any, have been discovered that support the continuation of this restrictive REMS. Mifepristone is of significant public health importance given its FDA-approved indication for use, in combination with misoprostol, to safely terminate early pregnancies.

Disclosure is also in the public interest pursuant to 21 CFR § 20.46(b)(3) and (4) because I plan to disseminate the information I obtain from this request to the public through publication in widely distributed, high-impact, peer-reviewed medical and public health journals, as well as other media. I have an established track record of such publications, including publications based on FOIA requests to FDA. Exemplary high-impact publications based on my investigations include

- Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products. *JAMA.* 2019;321(7):676–685. doi:10.1001/jama.2019.0235
- Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med.* 2018;178(11):1451–1457. doi:10.1001/jamainternmed.2018.3931
- Qato DM, Alexander GC. Post-Marketing Drug Safety and the Food and Drug Administration's Risk Evaluation and Mitigation Strategies. *JAMA*. 2011;306:1595-1596.

The requester has no commercial interest in the information sought:

I have no commercial interest in the information sought. 45 C.F.R. § 5.54(b)(3). I am not in the business of developing or selling new drugs or biologics, and I do not stand to make a profit from the disclosure of the requested information. I have no commercial interest in these records, but rather I aim to facilitate and conduct rigorous, objective, and fair evaluation of the information sought in furtherance of public knowledge and public health.

For these reasons, a public interest waiver of fees is appropriate here. I therefore respectfully request that all fees related to the search, review, and duplication of the requested records be waived. If the search and review fees will not be waived, I ask that you contact me at the email address listed below should the estimated fees resulting from this request exceed $100.

Conclusion

Pursuant to applicable statutes and regulations, I anticipate a determination regarding expedited processing within 10 days. *See* 5 U.S.C. § 552(a)(6)(E)(ii); 21 C.F.R. § 20.44(a)(2).

If my request is denied in whole or in part, please justify all withholdings and redactions by reference to specific FOIA exemptions. I expect the release of all segregable portions of otherwise exempt material, see 5 U.S.C. § 552(b), and reserve the right to appeal a decision to withhold any information or deny a waiver of fees.

Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street W6035
Baltimore, MD 21205
Phone: 410 955 8168
Fax: 410 955 0863
Email: galexan9@jhmi.edu

Please communicate any questions you may have by phone or email, rather than regular mail. Also, if the requested records cannot be provided by email, please notify me as soon as they are available and I will consider arranging to collect them by courier to avoid additional delay.

Your prompt attention to this request is greatly appreciated.

Respectfully,

G Caleb Alexander

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine

EXHIBIT D

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Drug Safety and Effectiveness

May 21, 2019

Food and Drug Administration
Division of Freedom of Information
Office of Shared Services
Office of Public Information and Library Services
12420 Parklawn Drive
ELEM-1029
Rockville, MD 20857

Re: FREEDOM OF INFORMATION ACT REQUEST

To Whom It May Concern:

My name is Caleb Alexander. I am a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health. This letter constitutes a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552, for records related to the FDA REMS program related to clopidogrel (Plavix).

Background

Risk Evaluation and Mitigation Strategies (REMS) of the Food and Drug Administration (FDA) represent an important regulatory tool that the FDA uses to optimize the safe use of approved therapeutics. As with any risk evaluation and mitigation program, the success of the REMS depends critically upon the quality and comprehensiveness of data that is used to guide regulatory decision-making. While the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversight of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

This request concerns the REMS for a particular drug, clopidogrel, marketed under the brand name Plavix by Bristol-Myers Squibb ("BMS"). Clopidogrel (Plavix) was subject to a product-specific REMS from February 2011 to May 2011 following evidence from post-marketing trials that found that Plavix lost its anti-platelet effects when used with drugs that inhibit cytochrome P450 2C19. Given the short duration of this REMS, we are interested in what data was submitted, if any, before, during or after the release of the REMS that would support its release.

Requested Records

I seek release of the following:

Any records relating to the REMS for clopidogrel (Plavix) from 2010 to 2013 including:

1. All correspondence between the FDA and BMS and any other manufacturers of this product including:
    a. FDA's initial evaluation assessing whether a REMS is needed for clopidogrel
    b. FDA's written correspondence explaining that a REMS is necessary
    c. BMS's or any other manufacturer of clopidogrel's proposed REMS plan, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. BMS's or any other manufacturer of clopidogrel's REMS supporting document, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the proposed REMS plan
    f. FDA's evaluation of the proposed supporting document
    g. BMS's proposed modifications, including elimination, to the approved REMS plan
    h. FDA's correspondence to BMS or any other manufacturer of clopidogrel approving or denying the modifications, including elimination, to the approved REMS plan
    i. Any explanations by the FDA regarding their final decision about the REMS plan
2. All REMS Assessment Reports submitted by BMS or any other manufacturer of clopidogrel to the FDA, including
    a. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to BMS
4. Any FDA REMS Modification Review reports sent to BMS or any other manufacturer of clopidogrel between February 2011 and May 2011
5. The FDA's evaluation assessing whether a REMS is needed for clopidogrel, including any FDA memoranda, and the written information used by FDA in the assessment, including any data
6. Any subsequent communication between the FDA and BMS or any other manufacturer of clopidogrel relating to all of the above

I request that all of these documents be produced in their native electronic formats with any attached metadata included, so long as such electronic files can be opened using standard commercially available software. If the files cannot be produced in this manner, I request that records be produced in an alternative electronic format that is text-searchable. With respect to databases, spreadsheets or similar organized sets of data, I request that the records be produced in .xls or .csv format. *See* 5 U.S.C. § 552(a)(3)(B).

Application for Expedited Processing

I request expedited processing for this request pursuant to 5 U.S.C. § 552(a)(6)(E) and 21 C.F.R. § 20.44(a)(2).

Expedited processing is appropriate here because a compelling need exists for the disclosure of the requested information. Shedding light on FDA's internal processes for instituting (and releasing) REMS is likely to have significant public health benefits, thereby reducing threats to the life or physical safety of all individuals using FDA-approved drugs. The public interest is heightened because REMS are implemented for unusually dangerous drugs where there is a concern "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1. Clinicians, researchers, and the public at large will benefit from prompt access to the requested information, to ensure that the clopidogrel REMS and other REMS function well and that patients are not being harmed by REMS that are over- or underprotective.

Pursuant to 5 U.S.C. § 552(a)(6)(E)(vi) and 21 C.F.R. § 20.44(a)(2), I certify that the information in this request concerning the reasons for expedited processing is true and correct to the best of my knowledge and belief.

Application for Waiver of Fees

Pursuant to 5 U.S.C. § 552(a)(4)(A)(iii) and 21 C.F.R. § 20.46, I request waiver of fees incurred in connection with searching and copying in responding this request. I am requesting the waiver on the grounds that disclosure of the requested information is in the public interest because it is likely to contribute significantly to public understanding of the operations and activities of the government and is not primarily in the commercial interest of the requester.

Disclosure is in the public interest:

Disclosure is in the public interest pursuant to 21 CFR § 20.46(b)(1) and (2) because this request will shed light into operations or activities of the FDA that are not already public knowledge. As noted above in the Background section, while the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known about how REMS programs are developed, implemented, and monitored, including regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversite of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

The circumstances surrounding the FDA's decision to create a REMS for Plavix are not public knowledge. As noted above in the Background section, I am interested in the Plavix REMS documents to study the rationale that led to the FDA's decision to release Plavix from its REMS

after only 3 months. Given the short duration of this REMS, we are interested in what data was submitted, if any, before, during or after the release of the REMS that would support its release.

Disclosure is also in the public interest pursuant to 21 CFR § 20.46(b)(3) and (4) because I plan to disseminate the information I obtain from this request to the public through publication in widely distributed, high-impact, peer-reviewed medical and public health journals, as well as other media. I have an established track record of such publications, including publications based on FOIA requests to FDA. Exemplary high-impact publications based on my investigations include

- Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products. *JAMA.* 2019;321(7):676–685. doi:10.1001/jama.2019.0235
- Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med.* 2018;178(11):1451–1457. doi:10.1001/jamainternmed.2018.3931
- Qato DM, Alexander GC. Post-Marketing Drug Safety and the Food and Drug Administration's Risk Evaluation and Mitigation Strategies. *JAMA*. 2011;306:1595-1596.

The requester has no commercial interest in the information sought:

I have no commercial interest in the information sought. 45 C.F.R. § 5.54(b)(3). I am not in the business of developing or selling new drugs or biologics, and I do not stand to make a profit from the disclosure of the requested information. I have no commercial interest in these records, but rather I aim to facilitate and conduct rigorous, objective, and fair evaluation of the information sought in furtherance of public knowledge and public health.

For these reasons, a public interest waiver of fees is appropriate here. I therefore respectfully request that all fees related to the search, review, and duplication of the requested records be waived. If the search and review fees will not be waived, I ask that you contact me at the email address listed below should the estimated fees resulting from this request exceed $100.

Conclusion

Pursuant to applicable statutes and regulations, I anticipate a determination regarding expedited processing within 10 days. *See* 5 U.S.C. § 552(a)(6)(E)(ii); 21 C.F.R. § 20.44(a)(2).

If my request is denied in whole or in part, please justify all withholdings and redactions by reference to specific FOIA exemptions. I expect the release of all segregable portions of otherwise exempt material, see 5 U.S.C. § 552(b), and reserve the right to appeal a decision to withhold any information or deny a waiver of fees.

Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street W6035
Baltimore, MD 21205
Phone: 410 955 8168
Fax: 410 955 0863
Email: galexan9@jhmi.edu

Please communicate any questions you may have by phone or email, rather than regular mail. Also, if the requested records cannot be provided by email, please notify me as soon as they are available and I will consider arranging to collect them by courier to avoid additional delay.

Your prompt attention to this request is greatly appreciated.

Respectfully,

G Caleb Alexander

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine

EXHIBIT E

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Drug Safety and Effectiveness

May 21, 2019

Food and Drug Administration
Division of Freedom of Information
Office of Shared Services
Office of Public Information and Library Services
12420 Parklawn Drive
ELEM-1029
Rockville, MD 20857

Re: FREEDOM OF INFORMATION ACT REQUEST

To Whom It May Concern:

My name is Caleb Alexander. I am a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health. This letter constitutes a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552, for records related to the FDA REMS program related to fluticasone propionate and salmeterol (Advair).

Background

Risk Evaluation and Mitigation Strategies (REMS) of the Food and Drug Administration (FDA) represent an important regulatory tool that the FDA uses to optimize the safe use of approved therapeutics. As with any risk evaluation and mitigation program, the success of the REMS depends critically upon the quality and comprehensiveness of data that is used to guide regulatory decision-making. While the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversight of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

This request concerns the REMS for a particular drug, fluticasone propionate and salmeterol, marketed under the brand name Advair by GlaxoSmithKline ("GSK"). Advair (salmeterol-fluticasone) is the most commonly used LABA (long acting beta agonist) that had a REMS consisting of both a medication guide and communication plan implemented in 2008 and released in 2012. The basis for this product-specific REMS was to mitigate the risk of pneumonia and asthma related death associated with Advair use. I am interested in REMS documents to study the rationale that led to the FDA's decision to release Advair from its REMS but maintain a boxed warning on Advair's label until it was removed in 2017.

Requested Records

I seek release of the following:

Any records relating to the REMS for Advair from 2007 to 2014 including:

1. All correspondence between the FDA and GSK and any other manufacturers of this product including:
    a. FDA's initial evaluation assessing whether a REMS is needed for Advair
    b. FDA's written correspondence explaining that a REMS is necessary
    c. GSK's and any other manufacturers of this product's proposed REMS plan, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. GSK's and any other manufacturers of this product's REMS supporting document, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the proposed REMS plan
    f. FDA's evaluation of the proposed supporting document
    g. GSK's and any other manufacturers of this product's proposed modifications, including elimination, to the approved REMS plan
    h. FDA's correspondence to GSK and any other manufacturers of this product approving or denying the modifications, including elimination, to the approved REMS plan
    i. Any explanations by the FDA regarding their final decision about the REMS plan
2. All REMS Assessment Reports submitted by GSK and any other manufacturers of this product to the FDA, including:
    a. the one-year Assessment Report submitted in or around April 2009
    b. the two-year Assessment Report submitted in or around April 2010
    c. the three-year Assessment Report submitted in or around April 2011
    d. the four-year Assessment Report submitted in or around April 2012
    e. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to GSK and any other manufacturers of this product between April 2008 and August 2012.
4. Any FDA REMS Modification Review reports sent to GSK and any other manufacturers of this product
5. The FDA's evaluation assessing whether a REMS is needed for Advair, including any FDA memoranda, and the written information used by FDA in the assessment, including any data.
6. Any subsequent communication between the FDA and GSK and any other manufacturers of this product relating to all of the above

I request that all of these documents be produced in their native electronic formats with any attached metadata included, so long as such electronic files can be opened using standard commercially available software. If the files cannot be produced in this manner, I request that records be produced in an alternative electronic format that is text-searchable. With respect to databases, spreadsheets or similar organized sets of data, I request that the records be produced in .xls or .csv format. *See* 5 U.S.C. § 552(a)(3)(B).

Application for Expedited Processing

I request expedited processing for this request pursuant to 5 U.S.C. § 552(a)(6)(E) and 21 C.F.R. § 20.44(a)(2).

Expedited processing is appropriate here because a compelling need exists for the disclosure of the requested information. Shedding light on FDA's internal processes for instituting (and releasing) REMS is likely to have significant public health benefits, thereby reducing threats to the life or physical safety of all individuals using FDA-approved drugs. The public interest is heightened because REMS are implemented for unusually dangerous drugs where there is a concern "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1. Clinicians, researchers, and the public at large will benefit from prompt access to the requested information, to ensure that the Advair REMS and other REMS function well and that patients are not being harmed by REMS that are over- or underprotective.

Pursuant to 5 U.S.C. § 552(a)(6)(E)(vi) and 21 C.F.R. § 20.44(a)(2), I certify that the information in this request concerning the reasons for expedited processing is true and correct to the best of my knowledge and belief.

Application for Waiver of Fees

Pursuant to 5 U.S.C. § 552(a)(4)(A)(iii) and 21 C.F.R. § 20.46, I request waiver of fees incurred in connection with searching and copying in responding this request. I am requesting the waiver on the grounds that disclosure of the requested information is in the public interest because it is likely to contribute significantly to public understanding of the operations and activities of the government and is not primarily in the commercial interest of the requester.

Disclosure is in the public interest:

Disclosure is in the public interest pursuant to 21 CFR § 20.46(b)(1) and (2) because this request will shed light into operations or activities of the FDA that are not already public knowledge. As noted above in the Background section, while the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known about how REMS programs are developed, implemented, and monitored, including regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk

mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversite of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

The circumstances surrounding the FDA's decision to create a REMS for Advair are not public knowledge, despite the drug's importance. As noted above in the Background section, I am interested in REMS documents to study the rationale that led to the FDA's decision to release Advair from its REMS but maintain a boxed warning on Advair's label until it was removed in 2017.

Disclosure is also in the public interest pursuant to 21 CFR § 20.46(b)(3) and (4) because I plan to disseminate the information I obtain from this request to the public through publication in widely distributed, high-impact, peer-reviewed medical and public health journals, as well as other media. I have an established track record of such publications, including publications based on FOIA requests to FDA. Exemplary high-impact publications based on my investigations include

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- Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med.* 2018;178(11):1451–1457. doi:10.1001/jamainternmed.2018.3931
- Qato DM, Alexander GC. Post-Marketing Drug Safety and the Food and Drug Administration's Risk Evaluation and Mitigation Strategies. *JAMA*. 2011;306:1595-1596.

The requester has no commercial interest in the information sought:

I have no commercial interest in the information sought. 45 C.F.R. § 5.54(b)(3). I am not in the business of developing or selling new drugs or biologics, and I do not stand to make a profit from the disclosure of the requested information. I have no commercial interest in these records, but rather I aim to facilitate and conduct rigorous, objective, and fair evaluation of the information sought in furtherance of public knowledge and public health.

For these reasons, a public interest waiver of fees is appropriate here. I therefore respectfully request that all fees related to the search, review, and duplication of the requested records be waived. If the search and review fees will not be waived, I ask that you contact me at the email address listed below should the estimated fees resulting from this request exceed $100.

Conclusion

Pursuant to applicable statutes and regulations, I anticipate a determination regarding expedited processing within 10 days. *See* 5 U.S.C. § 552(a)(6)(E)(ii); 21 C.F.R. § 20.44(a)(2).

If my request is denied in whole or in part, please justify all withholdings and redactions by reference to specific FOIA exemptions. I expect the release of all segregable portions of otherwise exempt material, see 5 U.S.C. § 552(b), and reserve the right to appeal a decision to withhold any information or deny a waiver of fees.

Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street W6035
Baltimore, MD 21205
Phone: 410 955 8168
Fax: 410 955 0863
Email: galexan9@jhmi.edu

Please communicate any questions you may have by phone or email, rather than regular mail. Also, if the requested records cannot be provided by email, please notify me as soon as they are available and I will consider arranging to collect them by courier to avoid additional delay.

Your prompt attention to this request is greatly appreciated.

Respectfully,

G Caleb Alexander

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine

EXHIBIT F

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Drug Safety and Effectiveness

May 21, 2019

Food and Drug Administration
Division of Freedom of Information
Office of Shared Services
Office of Public Information and Library Services
12420 Parklawn Drive
ELEM-1029
Rockville, MD 20857

Re: FREEDOM OF INFORMATION ACT REQUEST

To Whom It May Concern:

My name is Caleb Alexander. I am a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health. This letter constitutes a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552, for records related to the FDA REMS program related to varenicline.

Background

Risk Evaluation and Mitigation Strategies (REMS) of the Food and Drug Administration (FDA) represent an important regulatory tool that the FDA uses to optimize the safe use of approved therapeutics. As with any risk evaluation and mitigation program, the success of the REMS depends critically upon the quality and comprehensiveness of data that is used to guide regulatory decision-making. While the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversight of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

This request concerns the REMS for a particular drug, varenicline, marketed under the brand name Chantix by Pfizer. Chantix (Varenicline) was subject to a REMS from 2009 to 2016 that required a medication guide. From 2009 to 2016, the FDA also required a black box warning on the safety label of Chantix about the risk of serious neuropsychiatric events, including suicidal ideation, associated with its use. I am interested in the Chantix REMS documents to study the rationale that led to the FDA's decision to release Chantix from its REMS and how the implementation of a medication guide impacted its safe use. I hope to learn the extent and quality of data sufficient to

release a drug from its REMS requirement and are interested in discussions between the FDA and sponsors about the quality of presented data and how they defined acceptable risk.

Requested Records

I seek release of the following:

Any records relating to the REMS for varenicline (Chantix) including from 2008 through 2018:

1. All correspondence between the FDA and Pfizer or any other manufacturer of varenicline including:
    a. FDA's initial evaluation assessing whether a REMS is needed for varenicline
    b. FDA's written correspondence explaining that a REMS is necessary
        i. including the May 2008 FDA letter to Pfizer requiring a REMS and issuing a post marketing requirement for a clinical trial to assess the known serious risk of neuropsychiatric adverse events related to the use of varenicline products
    c. Pfizer's or any other manufacturer of varenicline's proposed REMS plan, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. Pfizer's or any other manufacturer of varenicline's REMS supporting document, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the proposed REMS plan
    f. FDA's evaluation of the proposed supporting document
    g. Pfizer's proposed modifications, including elimination, to the approved REMS plan
        i. including those submitted on November 8, 2013 and September 3, 2014
    h. FDA's correspondence to Pfizer or any other manufacturer of varenicline's approving or denying the modifications, including elimination, to the approved REMS plan
    i. Any explanations by the FDA regarding their final decision about the REMS plan
2. All REMS Assessment Reports submitted by Pfizer or any other manufacturer of varenicline's to the FDA, including:
    a. The 18-month Report submitted in or around April 2011, the 3-year Report submitted in or around October 2012, and the 7-year Report submitted in or around October 2016.
    b. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to Pfizer or any other manufacturer of varenicline's

4. Any FDA REMS Modification Review reports sent to Pfizer or any other manufacturer of varenicline's between October 2009 and December 2016, including the modification approved on October 15, 2014
5. The FDA's evaluation assessing whether a REMS is needed for varenicline, including any FDA memoranda, and the written information used by FDA in the assessment, including any data.
6. Any subsequent communication between the FDA and Pfizer or any other manufacturer of varenicline's relating to all of the above

I request that all of these documents be produced in their native electronic formats with any attached metadata included, so long as such electronic files can be opened using standard commercially available software. If the files cannot be produced in this manner, I request that records be produced in an alternative electronic format that is text-searchable. With respect to databases, spreadsheets or similar organized sets of data, I request that the records be produced in .xls or .csv format. *See* 5 U.S.C. § 552(a)(3)(B).

Application for Expedited Processing

I request expedited processing for this request pursuant to 5 U.S.C. § 552(a)(6)(E) and 21 C.F.R. § 20.44(a)(2).

Expedited processing is appropriate here because a compelling need exists for the disclosure of the requested information. Shedding light on FDA's internal processes for instituting (and releasing) REMS is likely to have significant public health benefits, thereby reducing threats to the life or physical safety of all individuals using FDA-approved drugs. The public interest is heightened because REMS are implemented for unusually dangerous drugs where there is a concern "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1. Clinicians, researchers, and the public at large will benefit from prompt access to the requested information, to ensure that the varencicline REMS and other REMS function well and that patients are not being harmed by REMS that are over- or underprotective.

Pursuant to 5 U.S.C. § 552(a)(6)(E)(vi) and 21 C.F.R. § 20.44(a)(2), I certify that the information in this request concerning the reasons for expedited processing is true and correct to the best of my knowledge and belief.

Application for Waiver of Fees

Pursuant to 5 U.S.C. § 552(a)(4)(A)(iii) and 21 C.F.R. § 20.46, I request waiver of fees incurred in connection with searching and copying in responding this request. I am requesting the waiver on the grounds that disclosure of the requested information is in the public interest because it is likely to contribute significantly to public understanding of the operations and activities of the government and is not primarily in the commercial interest of the requester.

Disclosure is in the public interest:

Disclosure is in the public interest pursuant to 21 CFR § 20.46(b)(1) and (2) because this request will shed light into operations or activities of the FDA that are not already public knowledge. As noted above in the Background section, while the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known about how REMS programs are developed, implemented, and monitored, including regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversite of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

The circumstances surrounding the FDA's decision to create a REMS for varenicline are not public knowledge. As noted above in the Background section, I am interested in the Chantix REMS documents to study the rationale that led to the FDA's decision to release Chantix from its REMS and how the implementation of a medication guide impacted its safe use. I hope to learn the extent and quality of data sufficient to release a drug from its REMS requirement and are interested in discussions between the FDA and sponsors about the quality of presented data and how they defined acceptable risk.

Disclosure is also in the public interest pursuant to 21 CFR § 20.46(b)(3) and (4) because I plan to disseminate the information I obtain from this request to the public through publication in widely distributed, high-impact, peer-reviewed medical and public health journals, as well as other media. I have an established track record of such publications, including publications based on FOIA requests to FDA. Exemplary high-impact publications based on my investigations include

- Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products. *JAMA.* 2019;321(7):676–685. doi:10.1001/jama.2019.0235
- Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med.* 2018;178(11):1451–1457. doi:10.1001/jamainternmed.2018.3931
- Qato DM, Alexander GC. Post-Marketing Drug Safety and the Food and Drug Administration's Risk Evaluation and Mitigation Strategies. *JAMA*. 2011;306:1595-1596.

The requester has no commercial interest in the information sought:

I have no commercial interest in the information sought. 45 C.F.R. § 5.54(b)(3). I am not in the business of developing or selling new drugs or biologics, and I do not stand to make a profit from the disclosure of the requested information. I have no commercial interest in these records, but rather I aim to facilitate and conduct rigorous, objective, and fair evaluation of the information sought in furtherance of public knowledge and public health.

For these reasons, a public interest waiver of fees is appropriate here. I therefore respectfully request that all fees related to the search, review, and duplication of the requested records be waived. If the search and review fees will not be waived, I ask that you contact me at the email address listed below should the estimated fees resulting from this request exceed $100.

Conclusion

Pursuant to applicable statutes and regulations, I anticipate a determination regarding expedited processing within 10 days. *See* 5 U.S.C. § 552(a)(6)(E)(ii); 21 C.F.R. § 20.44(a)(2).

If my request is denied in whole or in part, please justify all withholdings and redactions by reference to specific FOIA exemptions. I expect the release of all segregable portions of otherwise exempt material, see 5 U.S.C. § 552(b), and reserve the right to appeal a decision to withhold any information or deny a waiver of fees.

Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street W6035
Baltimore, MD 21205
Phone: 410 955 8168
Fax: 410 955 0863
Email: galexan9@jhmi.edu

Please communicate any questions you may have by phone or email, rather than regular mail. Also, if the requested records cannot be provided by email, please notify me as soon as they are available and I will consider arranging to collect them by courier to avoid additional delay.

Your prompt attention to this request is greatly appreciated.

Respectfully,

G Caleb Alexander

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine

EXHIBIT G

Subject: FDA Receipt of FOI Request
Date: Thursday, May 23, 2019 at 8:33:35 AM Eastern Daylight Time
From: FDA_FOI@fda.gov
To: Caleb Alexander

Note: Do NOT reply directly to this E-mail

Johns Hopkins Bloomberg School of Public Health G. Caleb Alexander

Re: Confirmation # FDA1953450
In Reply refer to: 2019-4472

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

REMS for zolpidem(Zolpimist/Edluar) from 2007 through 2013

Original Subject: Any records relating to the REMS for zolpidem(Zolpimist/Edluar) from 2007 through 2013 including: 1. All correspondence between the FDA and Aytu, Meda or any NDA for zolpidem (Zolpimist, Eluar) and any other manufacturers of this product 2. All REMS Assessment Reports submitted by Aytu, Meda and any other manufactuer of this product to the FDA 3. All FDA reviews of REMS Assessment Reports returned to Aytu, Meda and any other manufactuer of this produc between December 2008 and September 2011. ...

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm. If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at (301) 796-8982 or write to us at:

Division of Freedom of Information, U.S. Food and Drug Administration
5630 Fishers Lane, Room 1035
Rockville, MD 20857
Fax:(301)827-9267

You also have the right to seek dispute resolution services from:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane, Room 1050
Rockville, MD 20857

E-Mail: FDAFOIA@fda.hhs.gov and/or:

Office of Government Information Services
National Archives and Administration
8601 Adelphi Road ? OGIS
College Park, MD 20740-6001

Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

EXHIBIT H

Subject: FDA Receipt of FOI Request
Date: Thursday, May 23, 2019 at 8:24:50 AM Eastern Daylight Time
From: FDA_FOI@fda.gov
To: Caleb Alexander

Note: Do NOT reply directly to this E-mail

Johns Hopkins Bloomberg School of Public Health G. Caleb Alexander

Re: Confirmation # FDA1953444
In Reply refer to: 2019-4465

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

REMS for prasugrel (Effient) from 2008 to 2014

Original Subject: Any records relating to the REMS for prasugrel (Effient) from 2008 to 2014 including: 1. All correspondence between the FDA and Lilly and any other manufacturer of this product 2. All REMS Assessment Reports submitted by Lilly and any other manufacturer of this product to the FDA 3. All FDA reviews of REMS Assessment Reports returned to Lilly and any other manufacturer of this product, including an review of the report due January 31, 2011 4. Any FDA REMS Modification Review reports sent to Lill...

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm. If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at (301) 796-8982 or write to us at:

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Fax:(301)827-9267

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Rockville, MD 20857

E-Mail: FDAFOIA@fda.hhs.gov and/or:

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National Archives and Administration
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College Park, MD 20740-6001

Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

EXHIBIT I

Subject: FDA Receipt of FOI Request
Date: Thursday, May 23, 2019 at 7:52:48 AM Eastern Daylight Time
From: FDA_FOI@fda.gov
To: Caleb Alexander

Note: Do NOT reply directly to this E-mail

Johns Hopkins Bloomberg School of Public Health G. Caleb Alexander

Re: Confirmation # FDA1953440
In Reply refer to: 2019-4457

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

REMS for Mifepristone/Mifeprex/RU-486 from 2010 to present

Original Subject: Any records relating to the REMS for Mifepristone/Mifeprex/RU-486 from 2010 to present including: 1. All correspondence between the FDA and Danco Laboratories and any other manufacturers of this product 2. All REMS Assessment Reports submitted by Danco Laboratories and any other manufacturers of this product to the FDA 3. All FDA reviews of REMS Assessment Reports returned to Danco Laboratories and any other manufacturers of this product 4. Any FDA REMS Modification Review reports sent to Danco...

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm. If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at (301) 796-8982 or write to us at:

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Rockville, MD 20857

E-Mail: FDAFOIA@fda.hhs.gov and/or:

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National Archives and Administration
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College Park, MD 20740-6001

Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

EXHIBIT J

Subject: FDA Receipt of FOI Request
Date: Thursday, May 23, 2019 at 7:51:34 AM Eastern Daylight Time
From: FDA_FOI@fda.gov
To: Caleb Alexander

Note: Do NOT reply directly to this E-mail

Johns Hopkins Bloomberg School of Public Health G. Caleb Alexander

Re: Confirmation # FDA1953439
In Reply refer to: 2019-4455

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

REMS for clopidogrel (Plavix) from 2010 to 2013

Original Subject: Any records relating to the REMS for clopidogrel (Plavix) from 2010 to 2013 including: 1. All correspondence between the FDA and BMS and any other manufacturers of this product 2. All REMS Assessment Reports submitted by BMS or any other manufacturer of clopidogrel to the FDA 3. All FDA reviews of REMS Assessment Reports returned to BMS 4. Any FDA REMS Modification Review reports sent to BMS or any other manufacturer of clopidogrel between February 2011 and May 2011 5. The FDA?s evaluation asse...

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm. If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at (301) 796-8982 or write to us at:

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Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

EXHIBIT K

Subject: FDA Receipt of FOI Request
Date: Wednesday, May 22, 2019 at 9:07:12 PM Eastern Daylight Time
From: FDA_FOI@fda.gov
To: Caleb Alexander

Note: Do NOT reply directly to this E-mail

Johns Hopkins Bloomberg School of Public Health G. Caleb Alexander

Re: Confirmation # FDA1953437
In Reply refer to: 2019-4428

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

Any records relating to the REMS for Advair from 2007 to 2014

Original Subject: Any records relating to the REMS for Advair from 2007 to 2014 including: 1. All correspondence between the FDA and GSK and any other manufacturers of this product 2. All REMS Assessment Reports submitted by GSK and any other manufacturers of this product to the FDA 3. All FDA reviews of REMS Assessment Reports returned to GSK and any other manufacturers of this product between April 2008 and August 2012. 4. Any FDA REMS Modification Review reports sent to GSK and any other manufacturers of thi...

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm. If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at (301) 796-8982 or write to us at:

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E-mail: ogis@nara.gov
Fax: 202-741-5769

EXHIBIT L

Subject: FDA Receipt of FOI Request
Date: Thursday, May 23, 2019 at 7:53:08 AM Eastern Daylight Time
From: FDA_FOI@fda.gov
To: Caleb Alexander

Note: Do NOT reply directly to this E-mail

Johns Hopkins Bloomberg School of Public Health G. Caleb Alexander

Re: Confirmation # FDA1953447
In Reply refer to: 2019-4458

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

REMS for varenicline (Chantix) including from 2008 through 2018

Original Subject: Any records relating to the REMS for varenicline (Chantix) including from 2008 through 2018: 1. All correspondence between the FDA and Pfizer or any other manufacturer of varenicline 2. All REMS Assessment Reports submitted by Pfizer or any other manufacturer of varenicline?s to the FDA 3. All FDA reviews of REMS Assessment Reports returned to Pfizer or any other manufacturer of varenicline?s 4. Any FDA REMS Modification Review reports sent to Pfizer or any other manufacturer of varenicline?s b...

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm. If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at (301) 796-8982 or write to us at:

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EXHIBIT M

FW: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

Udapi, Guruprasad <Guruprasad.Udapi@fda.hhs.gov>
Wed 3/3/2021 1:17 PM

To: Katherine Surma <katherine.surma@ylsclinics.org>

Good afternoon Ms. Surma,

CDER processes FOIAs in date order priority. There are currently approximately 200 requests with priority over the 2019 requests identified below. While the general estimate processing time for such complex requests is typically 24 months, it is dependent on the size and complexity of the FOIAs in the queue. I will notify you when the requests approach the top of the processing queue. Thank you.

From: Katherine Surma <katherine.surma@ylsclinics.org>
Sent: Friday, February 26, 2021 3:28 PM
To: Satchi, Sudarshini (Darshini) <Sudarshini.Satchi@fda.hhs.gov>
Cc: David Schulz <david.schulz@ylsclinics.org>; Stephen Stich <stephen.stich@YLSClinics.org>
Subject: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

Dear Ms. Darshini Satchi,

The Yale Law School Media Freedom and Information Access Clinic represents Dr. Caleb Alexander with respect to the following FOIA requests he has submitted to the FDA:

- 2019-4428
- 2019-4455
- 2019-4457
- 2019-4458
- 2019-4465
- 2019-4472

I am writing to you because the FDA has not yet provided any records in response to five of these six requests, all of which have been pending since May 2019. Last November, Dr. Alexander timely filed an administrative appeal to the one request, 2019-4458, for which he did receive a response; the FDA has yet to address that appeal, nearly four months later.

Dr. Alexander has retained us to pursue litigation if necessary to obtain these records, which should have been provided long ago. Before proceeding down that path, we are reaching out to you to see if there is not some way to get beyond this impasse without the time, effort and disruption of a lawsuit. Please let us know if we might

arrange a time talk with you about what can be done to unloosen responses without further delay. We look forward to hearing from you.

Sincerely,

Katherine Surma

J.D. Candidate 2021 | Yale Law School

Media Freedom and Information Access Clinic

EXHIBIT N

Re: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

Katherine Surma <katherine.surma@ylsclinics.org>

Thu 3/11/2021 11:45 AM

To: Udapi, Guruprasad <Guruprasad.Udapi@fda.hhs.gov>
Cc: David Schulz <david.schulz@ylsclinics.org>; Stephen Stich <stephen.stich@YLSClinics.org>

Dear Mr. Udapi,

Thank you for your recent correspondence regarding FOIA #2019-4428, #2019-4455, #2019-4457, #2019-4458, #2019-4465, and #2019-4472 filed by Dr. Caleb Alexander. We appreciated this information.

Might you be free to touch base by phone sometime over the coming week or two regarding this matter? Naturally, given the public health importance of the queries that Dr. Alexander proposes to examine, we would like to understand the process further, as well as to discuss with you potential means that might be used to resolve the current delay in processing his request.

Can you please let us know by Friday, March 19th whether you would be available, and if so, when might be convenient for you?

Thank you and best regards,

Katherine Surma
J.D. Candidate 2021 | Yale Law School
katherine.surma@yale.edu

From: Udapi, Guruprasad <Guruprasad.Udapi@fda.hhs.gov>
Sent: Wednesday, March 3, 2021 1:08 PM
To: Katherine Surma <katherine.surma@ylsclinics.org>
Subject: FW: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

Good afternoon Ms. Surma,

CDER processes FOIAs in date order priority. There are currently approximately 200 requests with priority over the 2019 requests identified below. While the general estimate processing time for such complex requests is typically 24 months, it is dependent on the size and complexity of the FOIAs in the queue. I will notify you when the requests approach the top of the processing queue. Thank you.

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Sent: Friday, February 26, 2021 3:28 PM
To: Satchi, Sudarshini (Darshini) <Sudarshini.Satchi@fda.hhs.gov>
Cc: David Schulz <david.schulz@ylsclinics.org>; Stephen Stich <stephen.stich@YLSClinics.org>
Subject: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

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- 2019-4455
- 2019-4457
- 2019-4458
- 2019-4465
- 2019-4472

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Sincerely,

Katherine Surma
J.D. Candidate 2021 | Yale Law School
Media Freedom and Information Access Clinic

EXHIBIT O

Re: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

Katherine Surma <katherine.surma@ylsclinics.org>

Mon 3/22/2021 6:30 AM

To: Udapi, Guruprasad <Guruprasad.Udapi@fda.hhs.gov>
Cc: David Schulz <david.schulz@ylsclinics.org>; Stephen Stich <stephen.stich@YLSClinics.org>

Dear Mr. Udapi,

We had hoped to receive a response from you by March 19th to discuss Caleb Alexander's FOIA requests, as we are perplexed by your March 3rd response to our inquiry.

In August 2019, the CDER FOIA Office told Dr. Alexander that his FOIA request 2019-4457 was then in the 4th or 5th position in the complex queue, and that a response might be expected in a matter of weeks or months, not years. We recently inquired about the status of his requests because it has been over 18 months since that estimate was provided, but no responses have been received. Your March 3rd email indicating that there are now about 200 requests that have priority over Dr. Alexander's requests was alarming, to say the least. This proposition is also impossible to reconcile with the fact that Dr. Alexander filed all six requests on the same day but received a response to just one of them (which an FDA FOIA officer told him was in the complex queue) approximately seven months ago.

We would very much prefer to sort out the status of Dr. Alexander's requests and develop an acceptable timeline for responses from the FDA without the need of litigation, but the inconsistent information that is being provided and the length of time that has already passed does not make sitting and waiting an acceptable option. Please let us know if we might arrange a time to speak with you about the status of these requests. We will do our best to make ourselves available at any time over the next couple of weeks that would work for you. We look forward to hearing from you.

Sincerely,

Katherine Surma
J.D. Candidate 2021 | Yale Law School
katherine.surma@yale.edu

From: Katherine Surma <katherine.surma@ylsclinics.org>
Sent: Wednesday, March 10, 2021 9:53 PM
To: Udapi, Guruprasad <Guruprasad.Udapi@fda.hhs.gov>
Cc: David Schulz <david.schulz@ylsclinics.org>; Stephen Stich <stephen.stich@YLSClinics.org>
Subject: Re: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

Dear Mr. Udapi,

Thank you for your recent correspondence regarding FOIA #2019-4428, #2019-4455, #2019-4457, #2019-4458, #2019-4465, and #2019-4472 filed by Dr. Caleb Alexander. We appreciated this information.

Might you be free to touch base by phone sometime over the coming week or two regarding this matter? Naturally, given the public health importance of the queries that Dr. Alexander proposes to examine, we would like to understand the process further, as well as to discuss with you potential means that might be used to resolve the current delay in processing his request.

Can you please let us know by Friday, March 19th whether you would be available, and if so, when might be convenient for you?

Thank you and best regards,

Katherine Surma
J.D. Candidate 2021 | Yale Law School
katherine.surma@yale.edu

From: Udapi, Guruprasad <Guruprasad.Udapi@fda.hhs.gov>
Sent: Wednesday, March 3, 2021 1:08 PM
To: Katherine Surma <katherine.surma@ylsclinics.org>
Subject: FW: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

Good afternoon Ms. Surma,

CDER processes FOIAs in date order priority. There are currently approximately 200 requests with priority over the 2019 requests identified below. While the general estimate processing time for such complex requests is typically 24 months, it is dependent on the size and complexity of the FOIAs in the queue. I will notify you when the requests approach the top of the processing queue. Thank you.

From: Katherine Surma <katherine.surma@ylsclinics.org>
Sent: Friday, February 26, 2021 3:28 PM
To: Satchi, Sudarshini (Darshini) <Sudarshini.Satchi@fda.hhs.gov>
Cc: David Schulz <david.schulz@ylsclinics.org>; Stephen Stich <stephen.stich@YLSClinics.org>
Subject: [EXTERNAL] Dr. Caleb Alexander 2019 FOIA Requests

Dear Ms. Darshini Satchi,

The Yale Law School Media Freedom and Information Access Clinic represents Dr. Caleb Alexander with respect to the following FOIA requests he has submitted to the FDA:

- 2019-4428
- 2019-4455
- 2019-4457
- 2019-4458
- 2019-4465
- 2019-4472

I am writing to you because the FDA has not yet provided any records in response to five of these six requests, all of which have been pending since May 2019. Last November, Dr. Alexander timely filed an administrative appeal to the one request, 2019-4458, for which he did receive a response; the FDA has yet to address that appeal, nearly four months later.

Dr. Alexander has retained us to pursue litigation if necessary to obtain these records, which should have been provided long ago. Before proceeding down that path, we are reaching out to you to see if there is not some way

to get beyond this impasse without the time, effort and disruption of a lawsuit. Please let us know if we might arrange a time talk with you about what can be done to unloosen responses without further delay. We look forward to hearing from you.

Sincerely,

Katherine Surma
J.D. Candidate 2021 | Yale Law School
Media Freedom and Information Access Clinic